REMARKS

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 1-6 were pending in this application and were rejected on various grounds. Claim 1 has been amended, and Claim 6 has been cancelled without prejudice or disclaimer for pursuit of their subject matter in latter continuation or divisional filings. Claims 1-5 are therefore present for further examination. The rejections to the pending claims are respectfully traversed.

The changes made to the Specification and Claims by the current amendment, including ~~deletions~~ and additions, are shown herein with deletions designated with a strikethrough and additions underlined.

Specification

The disclosure was objected to by the Examiner as containing browser-executable code. The specification has been amended to delete these hyperlinks.

Correction of Inventorship under 37 CFR §1.48(b)

Applicant requests that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

Rejection under 35 U.S.C. § 101

The Examiner rejected Claims 1-6 as lacking either a specific and substantial asserted utility or a well-established utility under 35 U.S.C. § 101. According to the Examiner, the specification does not disclose a function for antibodies against SEQ ID NO: 92. Further, while the PTO acknowledges that PRO1327 is more highly expressed in normal esophagus, stomach, lung, rectum and skin as compared to tumors in these same tissue types, the Examiner states that evidence of mere expression in a tissue is not tantamount to a showing of a role for the disclosed polynucleotides or polypeptides, and it is not clear that expression of the PRO1327 polypeptide is correlated with a specific change in physiology or with any cancer or proliferative disease. The PTO also takes the position that protein expression levels cannot be accurately predicted from the level of corresponding mRNA transcript, and therefore cannot be correlated to antibody binding.

Applicants respectfully disagree.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added.)

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Utility – Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the PTO must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the PTO has made a proper *prima facie* showing of lack of utility does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Substantial Utility - Applicants have established that the Gene Encoding the PRO1327 Polypeptide is Underexpressed in Certain Cancers and is Useful as a Diagnostic Tool

The PTO argues that the invention lacks specific and substantial utility because there is no necessary correlation between a specific disease state and the expression of the PRO1327 polypeptide. The utility of the claimed antibody depends upon whether or not the polypeptide it binds has utility and enablement. According to the PTO, the invention lacks utility, as it is not clear if the expression of the PRO1327 polypeptide is correlated with a specific change in physiology, for example, or with any cancer or proliferative disease.

The claims are directed to antibodies that bind to SEQ ID NO:92 (encoding PRO1327). The specification, in Example 18, discloses that the nucleic acid encoding PRO1327 (DNA66521-1583) is more highly expressed in normal esophagus, stomach, lung, rectum and skin as compared to tumors in these same tissue types.

The gene expression data in Example 18 was obtained using standard semi-quantitative PCR amplification reactions with cDNA libraries isolated from different human tumor and normal human tissue samples and analyzed by agarose gel electrophoresis so as to obtain a semi-quantitative determination of the level of expression of the PRO polypeptide-encoding nucleic acid in each reaction. Identification of the differential expression of the PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type rendered the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor, as well as therapeutically, as a target for the treatment of a tumor in a subject possessing such a tumor. Applicants submit herewith as Exhibit A the declaration of J. Christopher Grimaldi, an expert in

the field of cancer biology. The Declaration was originally submitted in co-pending application Serial No. 10/063,557. This declaration explains the importance of the data shown in Example 18, and how differential gene and protein expression studies are used to differentiate between normal tissue and cancer tissue (see Grimaldi Declaration, paragraph 7).

In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues. Mr. Grimaldi explains that:

> The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual. That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. (Paragraph 5).

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal." He explains that, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

Applicants further submit that it is generally well-understood in the art that in the majority of cases, gene expression correlates with levels of protein expression. In support of Applicants' position, Applicants submit herewith as Exhibit B a second declaration of J. Christopher Grimaldi, also originally submitted in co-pending application Serial No. 10/063,557.

As stated in paragraph 5 of this declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Scientists regularly rely on the results of gene expression to point the way to differential protein expression in disease and, in this case, cancer. Submitted herewith as Exhibit C is the declaration of Dr. Paul Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceeds this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the

encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Additional references support this position. For example, Orntoft et al. (submitted herewith as Exhibit D) studied transcript levels of 5600 genes in malignant bladder cancers which were linked to a gain/loss of chromosomal material using an array-based method. Orntoft et al. showed that there was a gene dosage effect and teach that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman et al. (submitted herewith as Exhibit E) showed, using CGH analysis and cDNA microarrays to compare DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there is "evidence of a prominent global influence of copy number changes on gene expression levels" (see page 6244, column 1, last paragraph). Additional supportive teachings are also provided by Pollack et al. (submitted herewith as Exhibit F) who studied a series of primary human breast tumors and found that "...62% of highly amplified genes show moderately or highly elevated expression, that DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels" (see column 1, abstract). Thus, these articles collectively teach that in general, there is a correlation between gene expression and mRNA expression.

Taken together, despite some teachings in the art of certain genes that do not fit within this paradigm which are exceptions rather than the rule, in the vast majority of cases, the combined teachings in the art, exemplified by Orntoft et al., Hyman et al. and Pollack et al. and the Grimaldi and Polakis declarations, overwhelmingly teach that gene expression influences protein levels. Thus, one of skill in the art would reasonably expect, in this instance, based on the gene expression data for the PRO1327 gene, that the PRO1327 protein is concomitantly under-expressed in tumors of the esophagus, stomach, lung, rectum and skin. Thus, Applicants submit that the PRO1327 protein and the antibodies against this protein have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use these molecules.

Claimed antibodies would have diagnostic utility even if the protein were not under-expressed

Even assuming *arguendo* that there is no correlation between gene expression and decreased protein expression for PRO1327, which Applicants submit is not true, an antibody to a polypeptide encoded by a gene that is under-expressed in cancer would still have a credible, specific and substantial utility. In support, Applicants submit herewith as Exhibit G the Declaration of Avi Ashkenazi, Ph.D., an expert in the field of cancer biology. Although Dr. Ashkenazi's Declaration focuses on gene and protein over-expression, these same principles apply to gene and protein under-expression. Dr. Ashkenazi's Declaration explains that:

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

This is echoed in paragraph 6 of the Grimaldi Declaration, Exhibit B. Mr. Grimaldi explains that:

> However, even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy.

Applicants submit that simultaneous testing of gene expression and gene product expression enables more accurate tumor classification, even if there is no positive correlation between the two. This leads to better determination of a suitable therapy.

This is further supported by the teachings in the article by Hanna and Mornin, submitted herewith as Exhibit H. The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes

testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Applicants have established that it is the general, accepted understanding in the art that there is a positive correlation between gene expression and protein expression. However, even when this is not the case, a polypeptide encoded by a gene that is differentially expressed in cancer would still have utility, as would its antibodies. Thus, Applicants have demonstrated another basis for supporting the asserted utility for the claimed antibodies.

Specific Utility

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of under-expression of PRO1327 nucleic acids in certain types of cancer cells along with the declarations discussed above provide a specific utility for the claimed antibodies to the protein. As stated above, the general, accepted understanding in the art is that if the expression of the gene is decreased in tumor cells, then the level of protein expression would also be decreased, and thus there is a correlation between nucleic acid levels and protein levels. This makes the PRO1327 protein and antibodies to it useful in detecting, diagnosing and further characterizing tumors. As stated above, even if protein levels are not decreased, the PRO1327 proteins and antibodies are still useful in further characterizing the type of tumor. All of the substantial utilities listed above are specific to the disclosed antibodies to the PRO1327 protein because there is evidence that PRO1327 is underexpressed in certain cancer cells compared to normal cells. This is not a general utility that would apply to the broad class of antibodies.

Even if a prima facie case of lack of utility had been established, it should be withdrawn on consideration of the totality of evidence

Applicants have provided several expert opinions supporting the utility of the present invention. Applicants submit that one of ordinary skill in the art would have no legitimate basis to doubt the credibility of the statements made by Mr. Grimaldi, and Drs. Polakis and Ashkenazi, and must treat as true the statements made by these experts. Applicants remind the Examiner that "Office personnel must accept an opinion from a qualified expert that is based upon relevant

facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." PTO Utility Examination Guidelines (2001).

Thus, given the totality of the evidence provided, Applicants submit that they have established a specific and substantial credible utility for the claimed antibodies as a diagnostic agent. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific and substantial credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the antibodies to the PRO1327 polypeptide set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejection under 35 U.S.C. §112, first paragraph – Enablement

The PTO rejected Claims 1-6 under 35 U.S.C. § 112, first paragraph, as not being enabled. The PTO argues that because the claimed invention is not supported by a substantial, specific and credible utility, the claims are not enabled so that one skilled in the art would know how to use the invention.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed antibodies. Applicants therefore request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph, based on a lack of utility for the claimed antibodies.

35 U.S.C. §112, second paragraph

The Examiner rejected Claims 1-6 as indefinite for the recitation of "an antibody that binds" and an "antibody that specifically binds". Claim 6 has been cancelled and Claim 1 amended to recite "specifically binds". Applicants submit that the term "specifically binds" has a well established meaning; it refers to the binding of an antibody to a particular polypeptide, where the antibody does not substantially bind to any other polypeptide. One of skill in the art would readily understand the language of the claims to mean that the claimed antibodies bind to specifically defined polypeptides (in this case the polypeptides of SEQ ID NO:92) but do not substantially bind to any other polypeptides. Since claim terms should be given their ordinary,

art-recognized meaning, the present rejection is believed to be misplaced, and should be withdrawn.

Conclusion

The present application is believed to be in condition for allowance, and action to that effect is respectfully solicited. Applicants invite the Examiner to call the undersigned if any issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Sept. 23, 2004

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